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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/689,550	10/21/2003	Pnina Fishman	FISHMAN10A	9316

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EXAMINER	
SANG, HONG	

ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 06/20/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/689,550	FISHMAN ET AL.	
	Examiner	Art Unit	
	Hong Sang	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) *6,11,14,15 and 19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7-10, 12, 13 and 16-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 March 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/22/04 & 4/5/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

RE: Fishman

1. Applicant's election without traverse of Group I (claims 3-5, 8-10, 12, 13 and 18) in the reply filed on 5/22/06 is acknowledged.

2. Claims 1, 2, 7, 16 and 17are linking claims which link groups I-VI together. Upon the allowance of the linking claim(s), the restriction requirement as to the linked inventions shall be withdrawn and any claim(s) depending from or otherwise including all the limitations of the allowable linking claim(s) will be entitled to examination in the instant application. Applicant(s) are advised that if any such claim(s) depending from or including all the limitations of the allowable linking claim(s) is/are presented in a continuation or divisional application, the claims of the continuation or divisional application may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application. Where a restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. In re Ziegler, 44 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

3. The information disclosure statements (IDS) filed on 3/22/04 and 4/5/04 have been considered. Signed copies are attached hereto.

4. Claims 1-19 are pending. Claims 6, 11, 14-15 and 19 are withdrawn from further consideration as being drawn to non-elected inventions.

5. Claims 1-5, 7-10, 12,13 and 16-18 are under examination.

Specification

6. The first line of the specification should be updated if applicant desires priority under 35 U.S.C. 1 19(e), 120, 121 and 3654c) based upon a previously filed application, specific reference to the earlier filed application must be made in the instant application. For benefit claims under 35 U.S.C. 120, 121 or 365(c), the reference must include the relationship (i.e., continuation, divisional, or continuation-in-part) of the applications. This should appear as the first sentence of the specification following the title, preferably as a separate paragraph unless it appears in an application data sheet. The status of nonprovisional parent application (s) (whether patented or abandoned) should also be included. If a parent application has become a patent, the expression "now Patent No.___" should follow the filing date of the parent application. If a parent application has become abandoned, the expression "now abandoned" should follow the filing date 6f the parent application.

For additional information, see United States Patent and Trademark Office OG Notices: 1268 OG 89 (18 March 2003) "Benefit of Prior-Filed Application". Appropriate correction is required.

Claim Rejections - 35 USC § 112, 2nd paragraph

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 3 and 8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 3 and 8 are rejected for reciting the term "a proliferative-related disease state" and "proliferative disease state". The meaning of the term "a proliferative-related disease state" and "proliferative disease state" is unclear. The instant specification defines proliferative disease as cancer or other proliferative disease such as psoriasis (page 9, lines 4-5). However, the specification does not teach the "other proliferative disease". There is no definition for "a proliferative-related disease state". The "proliferative-related disease state" reads on any diseases that cause a cancer or are resulted from a cancer.

Claim Rejections - 35 USC § 112, 1st paragraph

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claim 1-3, 7, 8, 12, 13, 16 and 17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of detecting a tumor in a subject, a method for determining the severity of a tumor in a subject and a method for determining whether a subject has a high probability of responding to a therapeutic treatment of a tumor comprising detecting the level of expression of A3AR in said tumor cells, does not reasonably provide enablement for a method of detecting any and all disease state in a subject, a

method for determining the severity of any and all disease state in a subject and a method for determining whether a subject has a high probability of responding to a therapeutic treatment of any and all disease state comprising detecting the level of expression of A3AR, or A3AR protein fragment in a sample of cells suspected of being in the disease state. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in In re Wands, 8 USPQ2d 1400 (CA FC 1988). Wands states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

Claims are drawn to a method of detecting a disease state in a subject, a method for determining the severity of a disease state in a subject and a method for determining whether a subject has a high probability of responding to a therapeutic treatment of a disease state by the administration of an A3AR agonist or an A3AR antagonist comprising detecting the level of expression of A3AR or A3AR protein fragment in a sample of cells suspected of being in the disease state. The invention is in a class of invention, which the CAFC has characterized

as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The breadth of the claims

The term "disease state" recited in the claims refers to any disease state. The "A3AR protein fragment" recited in claims 12 and 13 reads on any and all protein fragments of A3AR, as small as 2 amino acid residues.

Quantity of experimentation

The quantity of experimentation in this area is extremely large since there is significant variability in the level of expression of A3AR or A3AR protein fragments in different cells that are suspected of being in the disease state.

The unpredictability of the art and the state of the prior art

Fishman et al. (Curr. Topics Med. Chem. 2003, 3: 463-469, IDS) teach that A3AR expression level is found to be low in most body tissues other than testis, eosinophiles, basophils and neutrophils which all demonstrated massive expression (see page 463, left column, last paragraph). Fishman et al. teach that tumor cells such as human A375, melanoma, human Jurkat T cell lymphoma and murine pineal tumor cells, significantly express A3AR (see page 463, right column). Fishman et al. teach that activation of A3AR evokes different downstream signal transduction pathways which are cell type dependent and may attribute to the diverse responses (see page 463, last paragraph). Fishman

et al. teach that there is a debate in the literature regarding the pro or anti-inflammatory response medicated via A3AR activation in these cells; some reports recommend activating A3AR to block the inflammatory response while others favor the implementation of A3AR antagonists for the very same purpose (see page 464, left column, 4th paragraph). Therefore, the role that A3AR plays in different diseases is unpredictable. Moreover, activation of a receptor does not always correlate with the overexpression of a receptor. So far the art only teaches that A3AR is overexpressed in certain cancers such as melanoma, and lymphoma. The instant claims are drawn to a method of detecting a disease state by detecting the differential expression of the level of A3AR or A3AR protein fragments. While the art indicates that A3AR plays an important role in various physiological processes, it does not teach the A3AR is overexpressed in any diseases other than cancer.

The instant specification teaches that A3AR is differentially expressed in certain tumor cells compared to normal cells. However, there is no indication that A3AR is differentially expressed in any other disease states.

Furthermore, the "A3AR protein fragment", which encompasses fragments that are as small as 2 amino acid residues, most likely would not function as the A3AR protein. Detection of the "A3AR protein fragment" in a cell would not all represent the actual expression level of the A3AR protein.

Working examples and guidance in the specification

The specification discloses that the A3AR protein as well as mRNA are overexpressed in tumor cells, i.e. colon carcinoma, breast cancer and melanoma

(see Examples 1-5). However, there is no data in the specification indicating that A3AR is over expressed or under expressed in any other diseases. The specification fails to show that A3AR is differentially expressed in any other diseases. The specification does not teach any "A3AR protein fragments" are over expressed in any disease states including a cancer.

Level of skill in the art

The level of the skill in the art is deemed to be high

Conclusion

Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of the art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the presence of a working example which does not address the issue of the differential expression of A3AR in all diseases, and the lack of teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to

> be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. Claims 1-5, 7-10, 12, 13 and 16-18 are rejected under 35 U.S.C. 102(a) as being anticipated by Madi et al.(Drug Dev. Res., 2002, May 56(4): 560, IDS) in view of the teaching of Wei et al. (US Patent No. 6,063,376, Date of Paten 5/16/2000) and Keyomarsi et al. (US Patent No. 5,543,291, Date of Patent 8/6/1996).

Claims 1-5, 12 and 16-18 are drawn to a method of detecting a tumor in a subject, and a method for determining whether a subject has a high probability of responding to a therapeutic treatment of a tumor comprising (a) obtaining from the subject a sample of cells suspected of being a tumor; (b) detecting the level of expression of A3AR in said sample cells; and (c) comparing the level of said A3AR expression in said cells to a control level, the control level being the level of A3AR expression in normal cells of the same subject, or being a standard reference level for the A3AR expression which is indicative of a normal state, wherein a difference in the level between the control and the sampled cells is indicative of said tumor, or is indicative that the subject has a high probability of responding to a therapeutic treatment by an A3AR agonist or A3AR antagonist. Claim 7-10 and 13 are drawn to a method for determining the severity of a tumor in a subject, comprising a) obtaining from the subject a sample of cells suspected of being a tumor; (b) detecting the level of expression of A3AR in said sample cells; and (c) comparing the level of said A3AR expression in said cells with a predetermined calibration curve of the level of the A3AR; the values of the

calibration curve being correlated to the severity of the disease state, thereby determining the severity of the disease state of the subject.

Madi et al. teach detection of A3AR protein in melanoma and colon carcinoma cells using Western/Northern blot analysis and confocal microscopy and show that A3AR is highly expressed in these tumor cells.

Madi et al. do not teach comparing the level of A3AR protein expressed in melanoma and colon carcinoma cells with a control level, or to the values of a predetermined calibration curve. Madi et al. do not teach correlating the level of the expression of A3AR protein with the severity of the tumor. However, these deficiencies are made up for in the teaching of Wei and Keyomarsi.

Wei et al. teach a diagnostic assay for detecting altered levels of hdCK2 protein in various tissues since an over-expression of the proteins compared to normal control tissue samples may detect the presence of a disease or susceptibility to a disease related to malignancy, for example, tumors, wherein the assay includes a radioimmunoassay, competitive-binding assays, Western Blot analysis, ELISA assays and "sandwich" assay (see column 10, lines 10-19). Wei et al. teach a method of determining the amount of the protein present in a given volume of patient sample by comparing against a standard curve (see column 10, lines 40-42).

Keyomarsi et al. teach a method of staging of breast cancer by correlating the expression level of cyclin E protein to different stages of breast cancer; those from earlier stages showed cyclin E protein patterns similar to patterns from

normal adjacent tissue; those from end stages showed several bands with increasing intensity (see column 8, lines 56-67, and column 9, lines 1-10).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to measure the level of the expression of A3AR protein and thereafter detect a tumor or determine the severity of a tumor by comparing the level of the expression of A3AR to a normal control tissue or to a standard curve in view of the teaching of Madi, Wei and Keyomarsi. One would have been motivated to do so because Madi teaches that A3AR is highly expressed in tumors, Wei teaches that an over-expression of the proteins compared to normal control tissue samples may detect the presence of a tumor, and Keyomarsi et al. teach that the level of the expression of a protein can be used to stage of breast cancer. Moreover, one of ordinary skill in the art would have a reasonable expectation of success to do so because Wei teaches that A3AR is highly expressed in tumor cells, Wei teaches a method of detecting a tumor by measuring the level of the protein presented in tumor cells, and comparing said level to normal control tissue or a standard curve, and Keyomarsi et al. teach a method of correlating the level of the expression of a protein to different stages of breast tumor.

13. Claims 1-5, 7-10, 12, 13 and 16-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Baraldi et al. (US Patent No. 6,407,236B1, Data of Patent: 6/18/2002, earliest effective filing date at least 8/23/1999) in view of the teaching of Reeves et al. (Inflamm. Res. 2000, 49:666-672), Wei et al. (US

Patent No. 6,063,376, Date of Paten 5/16/2000) and Keyomarsi et al. (US Patent No. 5,543,291, Date of Patent 8/6/1996).

The interpretation of claims is set forth above (see paragraph 12 above).

Baraldi et al. teach a method for determining the presence of tumor cells which possess a high concentration of adenosine A3 receptors in a patient or in a cell sample comprising administering to the patient or to the sample a radiolabeled compound which can be detected following binding of the compound to tumor cells, allowing the compound to bind to tumor cells and detecting the radiolabel (see claims 38-39), wherein the compound selectively binds A3AR (see column 1, last paragraph, column 5, lines 7-10).

Baraldi et al. do not teach detecting adenosine A3 receptor protein or mRNA. Baraldi et al. do not teach comparing the level of the expression of A3AR to a control level or to the values of the calibration curve. Baraldi et al. do not teach correlating the level of the expression of A3AR protein with the severity of the tumor. However, these deficiencies are made up for in the teaching of Reeves, Wei and Keyomarsi.

Reeves et al. teach detection of A3AR protein by using a novel antibody specific-for the human A3AR (see page 667, left column).

Wei et al. teach a diagnostic assay for detecting altered levels of hdCK2 protein in various tissues since an over-expression of the proteins compared to normal control tissue samples may detect the presence of a disease or susceptibility to a disease related to malignancy, for example, tumors, wherein the assay includes a radioimmunoassay, competitive-binding assays, Western

Blot analysis, ELISA assays and "sandwich" assay (see column 10, lines 10-19). Wei et al. teach a method of determining the amount of the protein present in a given volume of patient sample by comparing against a standard curve (see column 10, lines 40-42).

Keyomarsi et al. teach a method of staging of breast cancer by correlating the expression level of cycline E protein to different stages of breast cancer; those from earlier stages showed cyclin E protein patterns similar to patterns from normal adjacent tissue; those from end stages showed several bands with increasing intensity (see column 8, lines 56-67, and column 9, lines 1-10).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to measure the level of the expression of A3AR protein and thereafter detect a tumor or determine the severity of a tumor by comparing the level of the expression of A3AR protein to a normal control tissue or to a standard curve in view of the teaching of Baraldi, Reeves. Wei and Keyomarsi. One would have been motivated to do so because Baraldi teaches a method for determining the presence of tumor cells which possess a high concentration of adenosine A3 receptors in a patient or in a cell sample comprising indirectly detecting the A3AR protein, i.e. detecting the radiolabeled agent that specifically binds to A3AR protein, and Reeve teaches a method of direct detecting the A3AR protein using an antibody that specifically binds to A3AR protein. Direct detection of a protein is more accurate than indirect detection because the binding agent used in the method of Baraldi may bind non-specifically to other cell components, which would result in inaccurate

measurement. Moreover, Wei teaches that an over-expression of the proteins compared to normal control tissue samples may detect the presence of a tumor, and Keyomarsi teaches that the level of the expression of a protein can be used to determine different stages of breast cancer. One of ordinary skill in the art would have a reasonable expectation of success to measure the level of the expression of A3AR protein and thereafter detect a tumor or determine the severity of a tumor by comparing the level of the expression of A3AR protein to a normal control tissue or to a standard curve because Baraldi teaches a method for determining the presence of tumor cells which possess a high concentration of adenosine A3 receptors in a patient or in a cell sample, Reeve teaches detecting A3AR protein using an antibody, Wei teaches a method of detecting a tumor by measuring the level of the protein presented in tumor cells, and comparing said level to normal control tissue or a standard curve, and Keyomarsi teaches a method of correlating the level of the expression of a protein to different stages of breast tumor.

Double Patenting

14. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686

F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

15. Claims 1, 2, 7, 12, 13, 16 and 17 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, 5 and 15 of copending Application No. 10/565,238. Although the conflicting claims are not identical, they are not patentably distinct from each other.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The interpretation of claims 1, 2, 7, 12, 13, 16 and 17 is set forth above (see paragraph 12).

Claims 1, 2, 5 and 15 of copending Application No. 10/565,238 are drawn to a method of determining an inflammatory state in a subject, a method for determining the severity of an inflammatory state in a subject, a method for selecting a subject from a certain inflammatory disease to receive anti-inflammatory therapeutic treatment that comprises administering to the subject an A3AR agonist, comprising determining the level of expression of A3AR in white blood cells from the subject, a high level of expression of A3AR compared

to a control being indicative of an inflammatory state in a subject. Because the "inflammatory state" recited in the claims 1, 2, 5 and 15 of copending Application No. 10/565,238 is a species of the genus of "a disease state" recited in the instant claims, the claims 1, 2, 5 and 15 of copending Application No. 10/565,238 anticipate the instant invention.

Conclusion

16. No claims are allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Hong Sang whose telephone number is (571) 272 8145. The examiner can normally be reached on 8:30am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry R. Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service

Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Hong Sang
Art Unit 1643
June 13, 2006

LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER